DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
P1370 B

19900 MacArthur Blvd., Ste 300
Irvine, California 92715-2445
Telephone (714) 798-7600

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 29, 1998

Marvin S. Samson, President
Institutional Division
Schein Pharmaceutical, Inc.
100 Campus Drive
Florham Park, NJ 07932

WARNING LETTER

Dear Mr. Samson:

WL-15-8

Inspections of your pharmaceutical manufacturing facility, Steris Laboratories, Inc., in Phoenix, Arizona, have revealed serious deviations from the Current Good Manufacturing Practice (CGMPs), Title 21, Code of Federal Regulations(CFR) Parts 210 and 211. The most recent inspection of your firm conducted from May 20, 1997 to July 25, 1997, by the Food and Drug Administration, revealed serious deviations from the CGMP regulations.

The deviations that cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act include:

1. Failure to establish scientifically sound test procedures to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. For example:

   Polymorph testing is required for each stability lot and finished product lot of the following suspension products: Dexamethasone Acetate Suspension 8 and 16 mg/ml; Estrone Aqueous Suspension 5 mg/ml; Hydrocortisone Acetate Suspension 25 mg/ml; Methylprednisolone Acetate 20, 40 and 80 mg/ml; Prednisolone Acetate Suspension 25 mg/ml; Testosterone Suspension 100 mg; Triamcinolone Acetonide Suspension 3 and 40 mg/ml; and Triamcinolone Diacetate Suspension 40 mg/ml.

   Although all lots of these products were not tested using methods that will detect polymorphic forms, they were released for distribution. The recent polymorphism studies your firm conducted on retain samples did not also include testing of actual stability samples.

2. Failure to validate analytical methods for many of the drug products that have been released and distributed. Examples of various products for which active assay and/or preservative assay methods have not been validated include: Vitamin B Complex, Lidocaine HCL Injection 1%, Testosterone Suspension USP, B-Complex with C and B-12 Injection, Trimethobenzamide HCL Injection, Gentamicin Sulfate Injection, Neomycin-Polymixin B Sulfates and Gramicidin Ophthalmic Solution, MorphineSulfate Injection, Levothyroxine Sodium for Injection, and Iron Dextran Injection.

3. Failure to validate the manufacturing processes for many of the products currently being distributed. Examples of products include: Vitamin B Complex 100, Estradiol Valerate Injection, USP, Edetate Disodium Injection, Dexpanthenol Injection,Trifluridine Ophthalmic Solution, Antilirium, Neomycin-Polymixin B Sulfates, Dicyclomine HCL Injection, Morphine Sulfate Injection CII, Diphenhydramine HCL, Pilocarpine HCL Ophthalmic Solution, Heparin Sodium Injection, Chorionic Gonadotropin for Injection, Gentamicin Sulfate Injection, Prochlorperazine Edisylate Injection and Levothyroxine Sodium for Injection.

   You indicated in the December 12, 1997 meeting with FDA that the manufacturing processes for forty-five per cent (45 %) of your product line has not been validated and validation for the remaining fifty-five per cent (55 %) is in process. Nevertheless, many of these products have been or continue to be distributed even though process validation has not been completed.

4. Failure to establish appropriate procedures to prevent objectionable microorganisms in drug products purporting to be sterile and failure to validate sterilization processes for many drug products. Examples include: the media bulk holding time simulation study that represents validation of your aseptic compounding process did not address time and number of aseptic transfers/manipulations to add ingredients to the sterile tank; and product specific sterile filter validation is not complete for many aseptically processed products.

5. Failure to follow-up and complete investigations of out-of-specification test results for finished products. Out-of-specification investigations have not been completed for up to one (1) year following the initial aberrant findings or were not thoroughly investigated. Additionally, you failed to extend investigations to review of batches of drug product that may have been associated with the specific failure or discrepancy. Examples include: investigations done on HEPA filters leaking in class 100 laminar flow hood and aseptic fill room areas were not extended to review of batches of drug products that may have been associated with the failure; and the investigation done for failed media fill lot 96Z230 in 10/96 did not extend to evaluation of all product lots that were aseptically compounded by the personnel involved in the media fill failure.

We acknowledge that your firm has submitted written responses dated July 25, 1997, October 1, 1997 and November 24, 1997, as well as provided information at the December 12, 1997 meeting with your firm. Your responses failed to provide a reasonable time frame for completion of test method validation and process validation for your firm's products.

In regard to items 1-5 above and observations I, II, IV and V of the July 25, 1997 FDA-483, we are concerned that there is no indication in your response that your firm plans to cease distributing the affected products until appropriate polymorph testing and validation of all analytical methods and manufacturing processes is completed. Any response to this letter should address your remedial action plan for all distributed and released product.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Current Good Manufacturing Practice regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts. In addition, as noted above, until adequate corrective actions have been taken, the Food and Drug Administration will not approve NDAs, ANDAs or requests for evaluation by government procurement agencies which your firm may have pending involving drug products which are affected by these violations.

We request that you take prompt action to correct these violations and all other violations of the Food, Drug and Cosmetic Act existing at your firm. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction, and/or prosecution.

You should notify this office in writing, within (fifteen) 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent the recurrence of similar violations and documentation to show that the correction was achieved. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within when the corrections will be completed.

You may contact Patricia Gupta, Investigator, at the Phoenix Resident Post (602) 829-7396 ext. 230, to discuss the content of this letter. Please address your response to Ms. Gupta at the following address:

Patricia Gupta
U.S. Food and Drug Administration
Phoenix Resident Posst
4615 E. Elwood St., Suite 200
Phoenix, AZ 85040-1948

We also ask that a copy of your response be forwarded to my attention at the following address:

Elaine C. Messa, District Director
U.S. Food and Drug Administration
Los Angeles District Office,
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612-2445

Sincerely,

Elaine C. Messa
District Director

cc: Mr. Gary R. Sielski, General Manager
Steris Laboratories, Inc.
520 N. 51st Avenue
Phoenix, AZ 85043